Another litter of 8 young receiving estrone treatment shows the same modifications induced by estradiol dipropionate in lesser degree.

Summary. Estradiol dipropionate and estrone have only a gynogenic action on the genital tracts of young opossums of either sex, contrasting in this respect with the male hormone testosterone propionate which exerts a dual effect. The most striking effects are exerted on the phallus and the epithelium of the urinogenital sinus. Müllerian ducts, although very immature, are definitely enlarged. Prostatic outgrowths are suppressed.

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A Study of the Fever-Producing Principle in the Typhoid Vaccine.*

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For a quarter of a century typhoid vaccine has been used clinically in what has been called non-specific protein-therapy.[1] The symptoms provoked by the intravenous injection of typhoid vaccine are shown in experiment 1 in Table I. They are fever, shivering (chills), leucopenia, and gastro-intestinal disturbances, such as vomiting and diarrhea. These are in the main, the symptoms mentioned by Hektoen[2] and Cecil[3] as following the intravenous injection of foreign proteins. These symptoms are also paralleled by those elicited in the "pyrogenic reaction" following the intravenous infusion of "pyrogenic" fluids and "pyrogenic" inulin as evinced in experiments 2 and 3 in the table.

The "pyrogen" of infusion-fluids was shown by Hort and Penfold[4] to pass through a Berkefeld candle. This was confirmed by Seibert,[5]

* We wish to thank Dr. Johannes H. Bauer of the Rockefeller Institute for instructions in the preparation and calibration of Elford-Bauer membranes used in this study.

1 Petersen, *The Newer Knowledge of Bacteriology and Immunology*, Jordan and Falk, The University of Chicago Press, 1928, p. 1086.

2 Hektoen, *J. A. M. A.*, 1935, **105**, 1765.

3 Cecil, *Ibid.*, 1935, **105**, 1846.

4 Hort and Penfold, *Brit. Med. J.*, 1911, **2**, 1589.

5 Seibert, *Am. J. Physiol.*, 1923, **67**, 90.

TABLE I.

Exp. No.	Material injected intravenously	Wt of dog, kg	Post-injection symptomatology						
			0 time	45 min	1½ hr	2 hr	3 hr	4 hr	5 hr
1	Whole typhoid vaccine, 1 cc	12.5	t—100.2 w—18.4	t—102.6 w—6.4	t—102.6 Shivering	t—103.2 Emesis Defecation	t—103.4 Shivering	t—102.8 Depressed	t—101.8
2	6% "pyrogenic" dextrose soln., 400 cc	11	t—101.6 w—17	t—102.8 w—2.3	t—104.5 Emesis	t—106 Defecation Shivering	t—104.5	t—103.2	t—102.4
3	10% "reactive" inulin 25 cc	17	t—101.8 w—16.5	t—104.4 w—8.8	t—104.8	t—105.3 Emesis Defecation	t—105.3	t—104.2	t—103.2
4	Berkefeld filtrate of typhoid vaccine, 1 cc	13	t—100.6 w—20.2	t—101.6 w—2.1 Shivering	t—104 Bloody stool	t—104.6 Emesis (bile) Bloody stool	t—104.4 Depressed	t—103.8	t—102
5	Typhoid broth, 1 cc	11.7	t—101.4 w—15	t—102 w—2.75 Emesis	t—103 Shivering Defecation	t—103.6 Shivering	t—104 Emesis	t—103.6 Depressed	t—102.8
6	Berkefeld filtrate of typhoid vaccine refiltered through 200 sec Zsigmondy, 18 cc	16	t—101.4 w—20	t—101.2 w—18	t—101.5 No symptoms	t—100.8	t—101	t—100.6	
7	Berkefeld filtrate of typhoid vaccine refiltered through Seitz, 30 cc	15	t—101.6 w—22.7	t—101.6 w—23	t—101 No symptoms	t—100.2	t—101.2		
8	Typhoid broth filtered through Seitz, 500 cc	14.5	t—101.4 w—12.6	t—101.6 w—15.5	t—101 No symptoms	t—101.2	t—101.2		

t—Rectal temperature, °F.
w—Leucocytes in thousands.

Banks,[6] and Co Tui, Schrift, McCloskey and Yates.[7, 8, 9] These last authors also showed that this "pyrogenic" principle was held back by a 200-second Zsigmondy filter as well as by an especially prepared asbestos filter pad of the type of Seitz Serum No. 3.

The purpose of the present study was to determine whether in addition to this symptomatic similarity, the fever-producing principle in typhoid vaccine exhibited filtration-characteristics similar to "pyrogen." The Berkefeld filtrate of broth in which *B. typhosus* had been grown for 48 hours (hereafter called typhoid broth) was likewise investigated. The test animal used in this study, as in our previous work, was the dog.

Berkefeld Filtration. Experiment 4 shows the clinical response to 1 cc of a Berkefeld filtrate of the typhoid vaccine used in Experiment 1. It will be seen that the clinical response is even more marked than in the case of the whole vaccine, the leucopenia being more profound, and the thermal rise higher. The gastro-intestinal disturbances were also more severe, with bile in the vomitus, and blood in the diarrheic stool.

Experiment 5 shows that typhoid broth, which, it will be remembered, is a Berkefeld filtrate, also contains the fever-producing principle.

It is thus clear that the fever-producing principle associated with *B. typhosus* is not bound to the bacterial bodies but may be separated from them by Berkefeld filtration. It may also be mentioned that the supernatant cell-free liquor of the centrifuged vaccine is likewise a potent fever-producer.

Membrane Filtration. Experiment 6 shows that the fever-producing principle in the Berkefeld filtrate of typhoid vaccine, like the "pyrogen" of inulin and infusion-fluids is held back by a 200-second Zsigmondy filter. That in typhoid broth, however, is not so removed. This may be explained on the basis of the increased permeability of collodion membranes caused by the presence of broth. This increased permeability was shown by Galloway and Elford[10] in the case of viruses. However, filtration through an isoporous membrane (Elford-Bauer), 100 mμ, removed the "pyrogenic" principle from the typhoid broth as well as from the typhoid-vaccine filtrate.

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[6] Banks, *Am. J. Clin. Path.*, 1934, **4**, 260.

[7] Co Tui, McCloskey, Schrift, and Yates, PROC. SOC. EXP. BIOL. AND MED., 1936, **35**, 297.

[8] Co Tui, Schrift, McCloskey, and Yates, PROC. SOC. EXP. BIOL. AND MED., 1937, **36**, 227.

[9] Co Tui, McCloskey, Schrift, and Yates, *J. A. M. A.*, 1937, **109**, 250.

[10] Galloway and Elford, *Brit. J. Exp. Path.*, 1931, **12**, 407.

Asbestos Pad Filtration. Experiments 7 and 8 show that the fever-producing principle in both typhoid broth and the Berkefeld filtrate of typhoid vaccine, is removed by filtration through a Seitz serum No. 3 filter. It may also be mentioned that recent experiments in our laboratory show that another asbestos filter pad, the Ertel No. 0, is equally as efficient in the removal of pyrogen as Seitz. In this respect, too, it reacts similarly to the "pyrogen" in infusion-fluids and inulin.[8]

Conclusions. 1. The fever-producing principle in typhoid vaccine and in broth in which *B. typhosus* has grown for 48 hours is not removed by Berkefeld filtration. The principle is, therefore, not bound to the bacterial bodies.

2. The principle is removed by a 200-second Zsigmondy filter and is, therefore, of approximately the same size as the principle previously found in reactive inulin and infusion-fluids.

3. Like "pyrogen" found in inulin and in infusion-fluids, it is removed by filtration through asbestos pads of the types of Seitz and Ertel.

4. On the basis of the clinical response provoked by intravenous injection, and the filtration characteristics, it is submitted that the fever-producing principle associated with *B. typhosus* and the "pyrogen" found in infusion-fluids and inulin are closely related substances.

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Effect of Electrolyte Disturbance on Resistance to Histamine Poisoning in Rats.

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Following suprarenalectomy there is a profound disturbance in electrolyte metabolism,[1, 2, 3] It is possible to reproduce an analogous disturbance in normal animals by introducing large amounts of isotonic glucose intraperitoneally and subsequently withdrawing the fluid.[4] The effect of this procedure on resistance to histamine was determined.

Method: Twenty cc of isotonic glucose solution was introduced into the peritoneal cavity of each of a number of rats and 4 hours

1 Marine, D., and Baumann, E. J., *Am. J. Physiol.*, 1927, **81**, 86.

2 Loeb, R. F., Atschley, D. W., Benedict, E. M., and Leland, J., *J. Exp. Med.*, 1933, **57**, 775.

3 Zwemer, R. L., and Truszkowski, R., *Science*, 1936, **83**, 558.

4 Gilman, A., *Am. J. Physiol.*, 1934, **108**, 662.